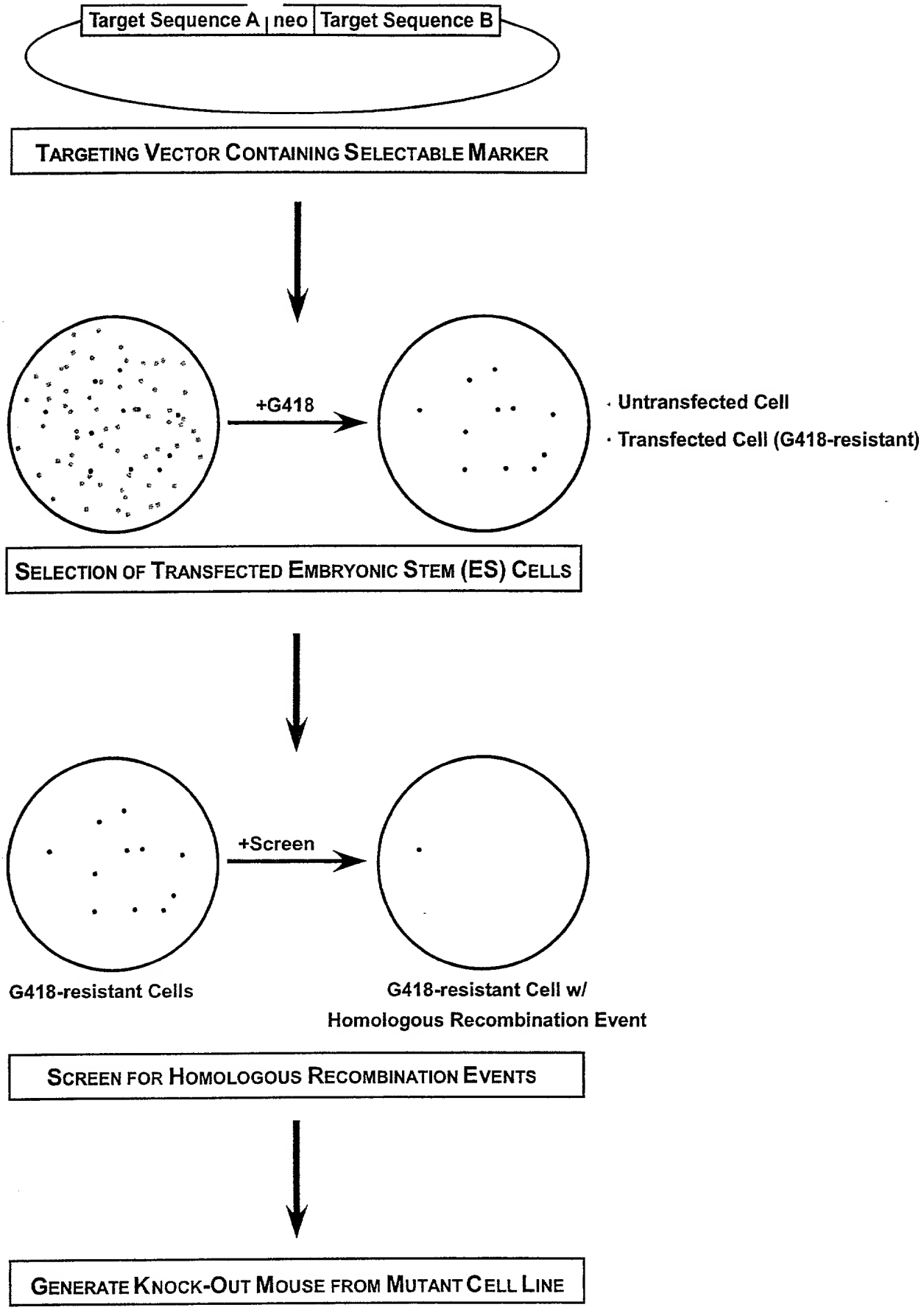
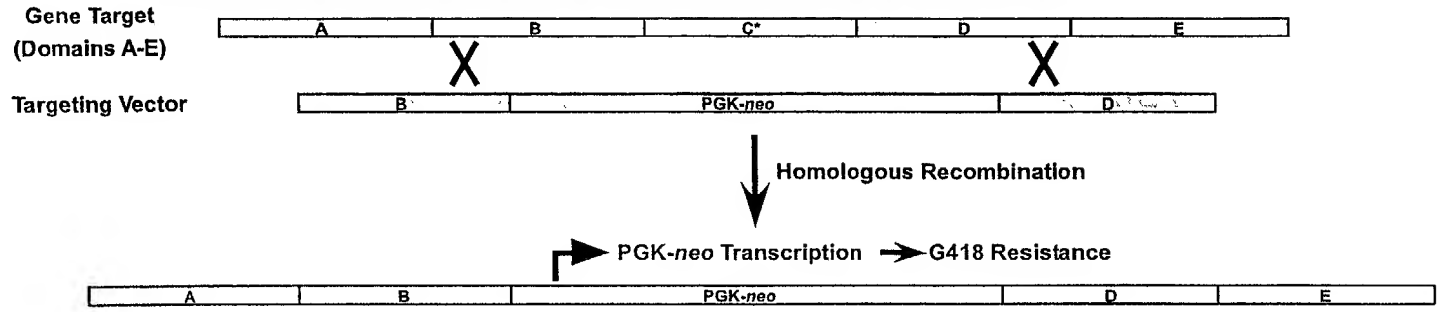
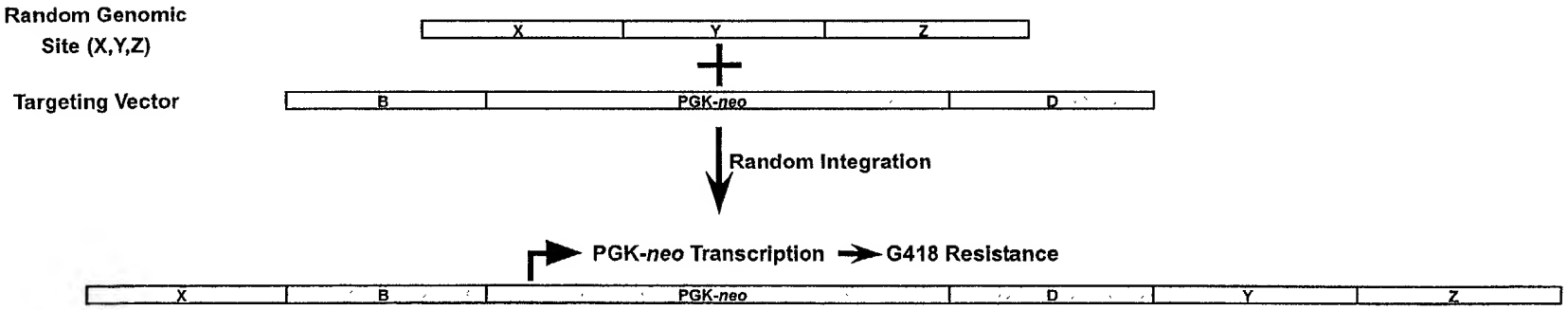

Target Sequence A
neo
Target Sequence B
TARGETING VECTOR CONTAINING SELECTABLE MARKER
+G418
· Untransfected Cell
· Transfected Cell (G418-resistant)
SELECTION OF TRANSFECTED EMBRYONIC STEM (ES) CELLS
+Screen
G418-resistant Cells
G418-resistant Cell w/
Homologous Recombination Event
SCREEN FOR HOMOLOGOUS RECOMBINATION EVENTS
GENERATE KNOCK-OUT MOUSE FROM MUTANT CELL LINE

Figure 1

A. Homologous Recombination: G418 Resistance, Targeting Vector Flanked by "A" and "E"



B. Random Integration: G418 Resistance, Targeting Vector Flanked by "X" and "Y"



DISTINGUISH EVENTS BY SCREENING MOLECULARLY (PCR & SOUTHERN)

Figure 2

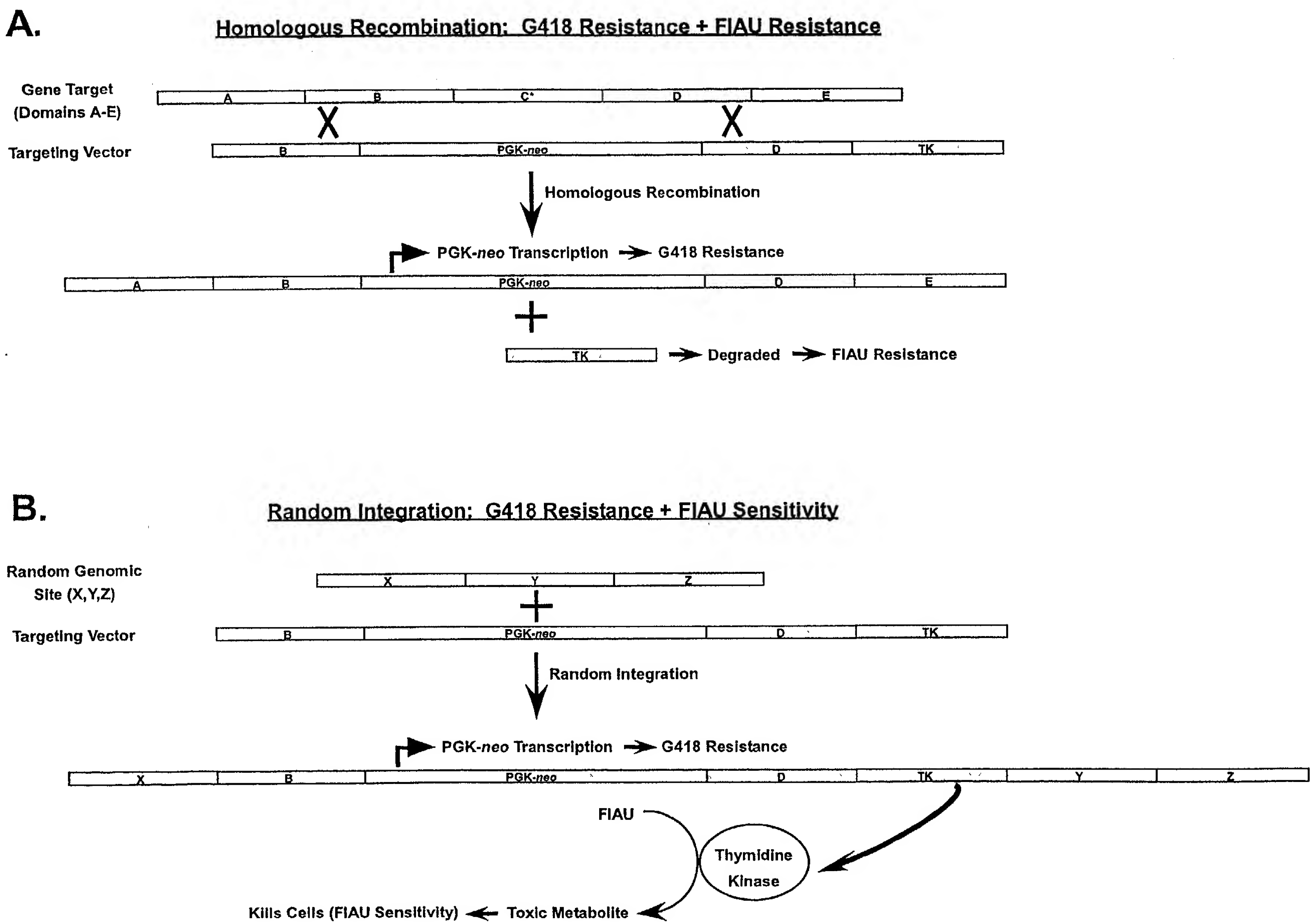

A.
Homologous Recombination: G418 Resistance + FIAU Resistance
Gene Target
(Domains A-E)
A
B
C*
D
E
X
X
Targeting Vector
B
PGK-neo
D
TK
Homologous Recombination
PGK-neo Transcription
G418 Resistance
A
B
PGK-neo
D
E
TK
Degraded
FIAU Resistance
B.
Random Integration: G418 Resistance + FIAU Sensitivity
Random Genomic
Site (X,Y,Z)
X
Y
Z
Targeting Vector
B
PGK-neo
D
TK
Random Integration
PGK-neo Transcription
G418 Resistance
X
B
PGK-neo
D
TK
Y
Z
FIAU
Thymidine
Kinase
Kills Cells (FIAU Sensitivity)
Toxic Metabolite

Figure 3

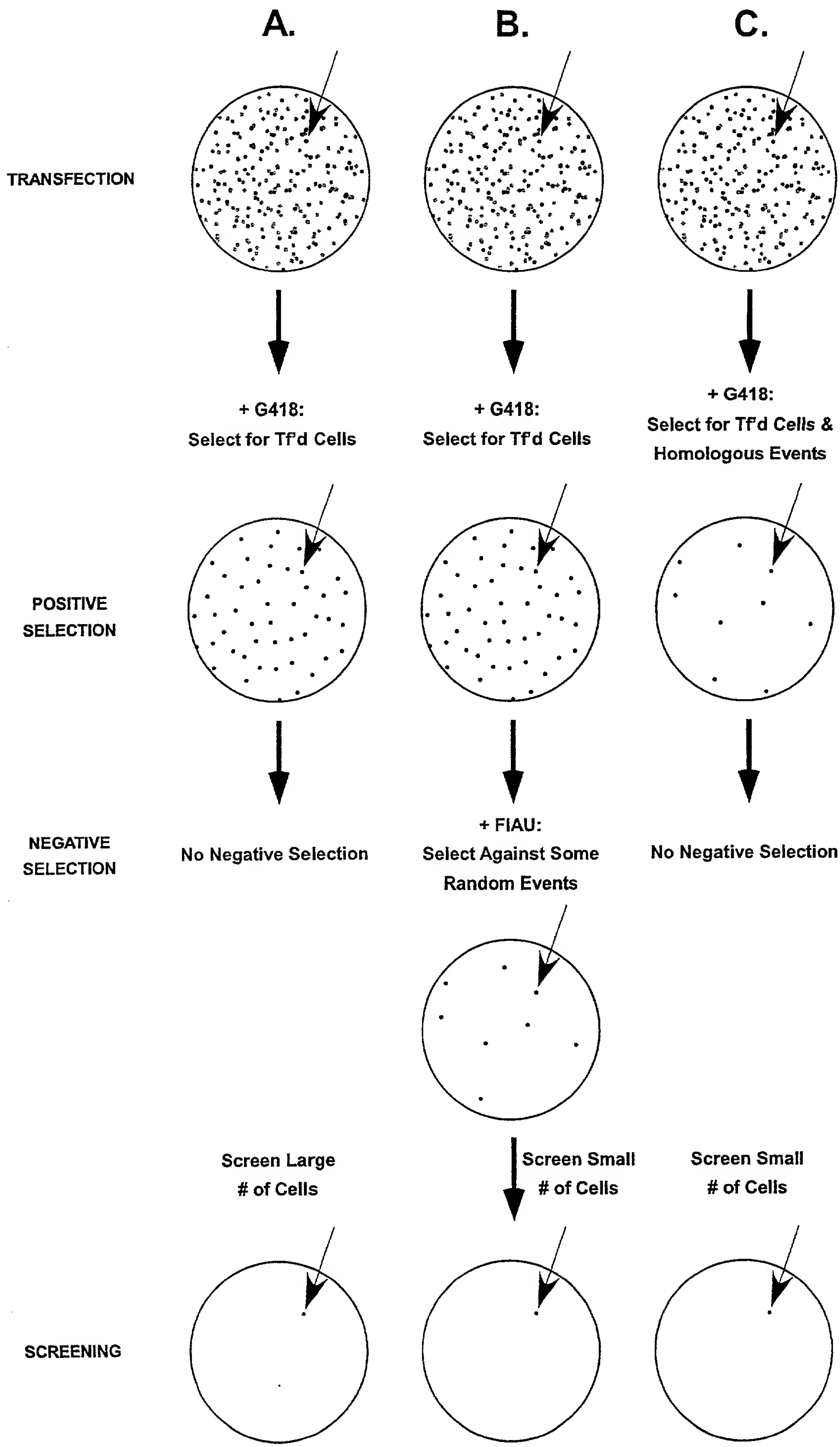

A.
B.
C.
TRANSFECTION
+ G418:
Select for Tf'd Cells
+ G418:
Select for Tf'd Cells
+ G418:
Select for Tf'd Cells &
Homologous Events
POSITIVE
SELECTION
NEGATIVE
SELECTION
No Negative Selection
+ FIAU:
Select Against Some
Random Events
No Negative Selection
Screen Large
# of Cells
Screen Small
# of Cells
Screen Small
# of Cells
SCREENING

Figure 4

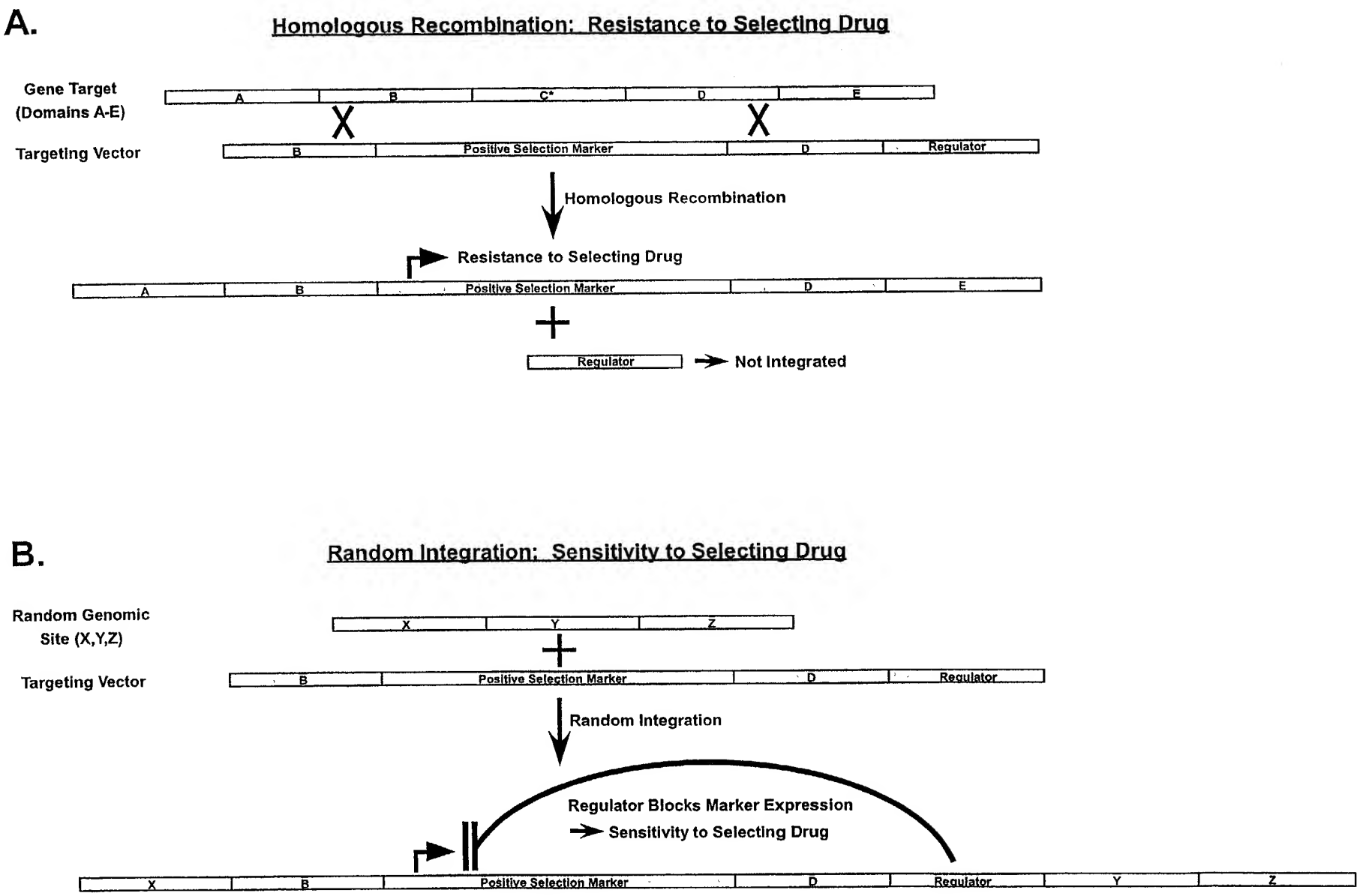


Figure 5

C3406:

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TTCTGCTATGTGGCGCGGTATTATCCCGTGTTGACGCCGGGCAAGAGCAACTCGGTCGCCGCATACACTATTCTCAGAATGACTTGGTT
GAGTACTCACCAGTCACAGAAAAGCATCTTACGGATGGCATGACAGTAAGAGAATTATGCAGTGCTGCCATAACCATGAGTGATAACAC
TGCGGCCAACTTACTTCTGACAACGATCGGAGGACCGAAGGAGCTAACCGCTTTTTTGCACAACATGGGGGATCATGTAACTCGCCTTG
ATCGTTGGGAACCGGAGCTGAATGAAGCCATACCAAACGACGAGCGTGACACCACGATGCCTGTAGCAATGGCAACAACGTTGCGCAAA
CTATTAACTGGCGAACTACTTACTCTAGCTTCCCGGCAACAATTAATAGACTGGATGGAGGCGGATAAAGTTGCAGGACCACTTCTGCG
CTCGGCCCTTCCGGCTGGCTGGTTTATTGCTGATAAATCTGGAGCCGGTGAGCGTGGGTCTCGCGGTATCATTGCAGCACTGGGGCCAG
ATGGTAAGCCCTCCCGTATCGTAGTTATCTACACGACGGGGAGTCAGGCAACTATGGATGAACGAAATAGACAGATCGCTGAGATAGGT
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CACCACACCCGCCGCGCTTAATGCGCCGCTACAGGGCGCGTAAAAGGATCTAGGTGAAGATCCTTTTTGATAATCTCATGACCAAAATC
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GTGTCGATGGTAGAACGAAGCGGCGTCGAAGCCTGTAAAGCGGCGGTGCACAATCTTCTCGCGCAACGCGTCAGTGGGCTGATCATTAA
CTATCCGCTGGATGACCAGGATGCCATTGCTGTGGAAGCTGCCTGCACTAATGTTCCGGCGTTATTTCTTGATGTCTCTGACCAGACAC
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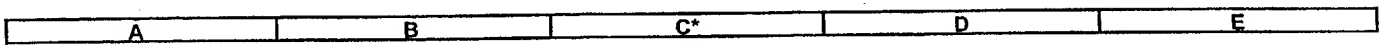
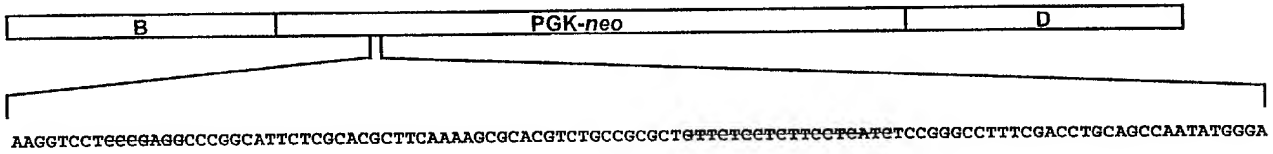
AGGCCCGCACCGATCGCCCTTCCCAACAGTTGCGCAGCCTGAATGGCGAATGGCGCTTCGCTTGGTAATAAAGCCCGCTTCGGCGGGCT
TTTTTTT

Figure 6A

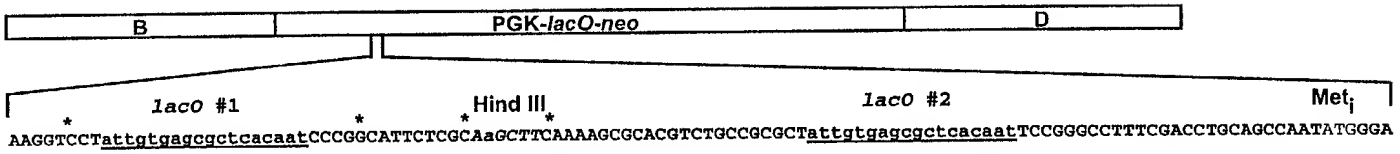
B. Gene Target (Domains A-E)



C. Targeting Vector: PGK-*neo*



D. Targeting Vector: PGK-*lacO-neo*



E. Targeting Vector: PGK-*lacO-neo* + NLS-*lacI*

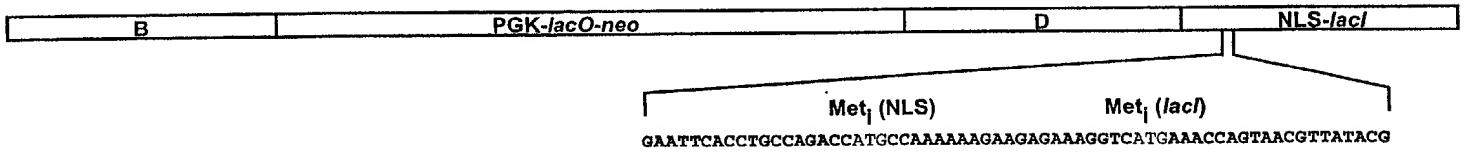


Figure 6 B-E

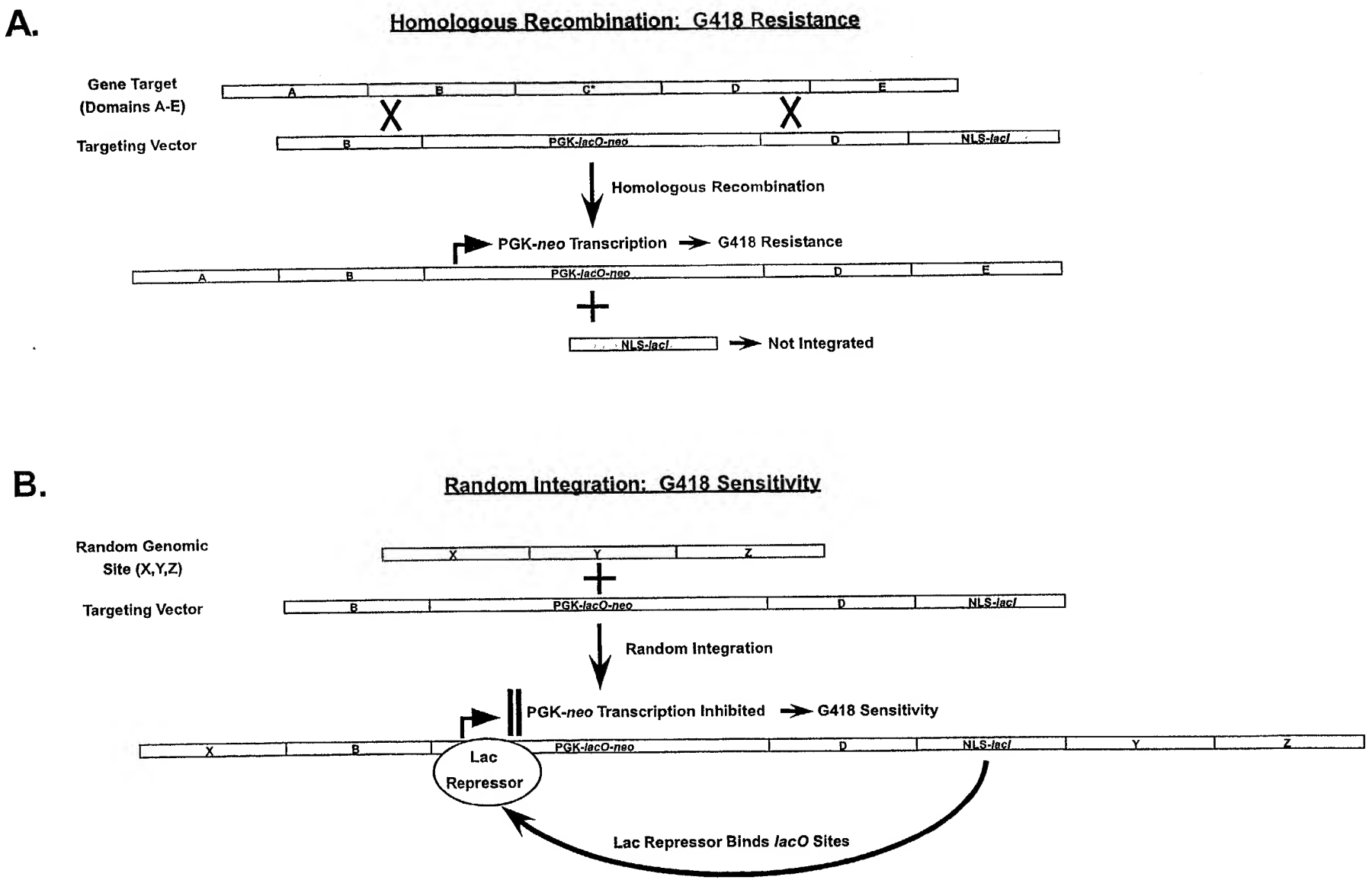


Figure 7

Oligo #	Sequence (5′ to 3′)
10164	CGGAATTCACCTGCCAGACCATGCCAAAAAAGAAGAGAAAGGTCATGAAACCAGTAACGTTATACG
10165	CGGAATTCTCACTGCCCGCTTTCCAGTCG
10218	GCATTCTCGCAAGCTTCAAAAGCGCACGTCTGCCGCGCTATTGTGAGCGCTCACAATTCCGGGCCTTTCGACCTG
9959	TCATCAATTTCTGCAGAC
10219	TGCGCTTTTGAAGCTTGCGAGAATGCCGGGATTGTGAGCGCTCACAATAGGACCTTCGCGCCCGCC
4201	CAGGAAACAGCTATGAC

Figure 8

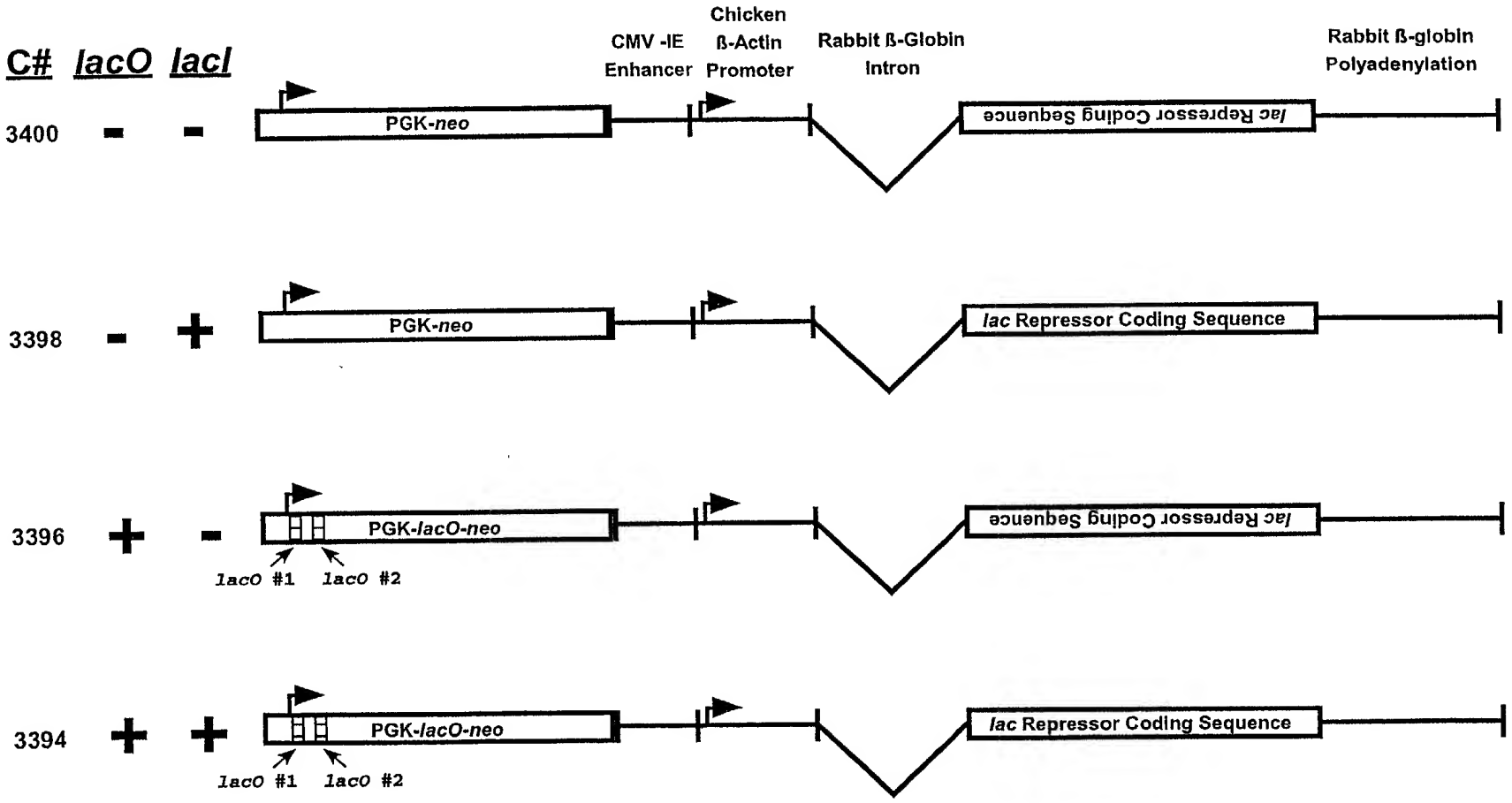


Figure 9

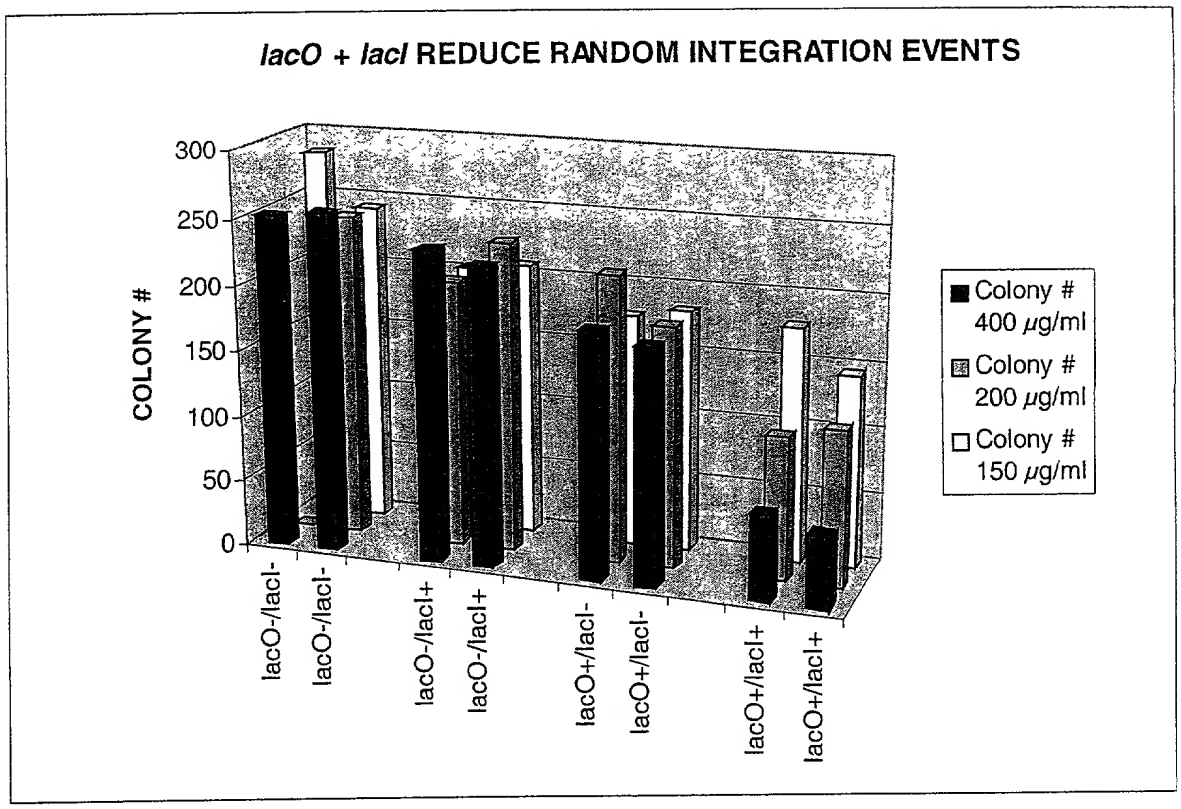

lacO + lacI REDUCE RANDOM INTEGRATION EVENTS
COLONY #
300
250
200
150
100
50
0
lacO-/lacI-
lacO-/lacI-
lacO-/lacI+
lacO-/lacI+
lacO+/lacI-
lacO+/lacI-
lacO+/lacI+
lacO+/lacI+
Colony # 400 µg/ml
Colony # 200 µg/ml
Colony # 150 µg/ml

Figure 10

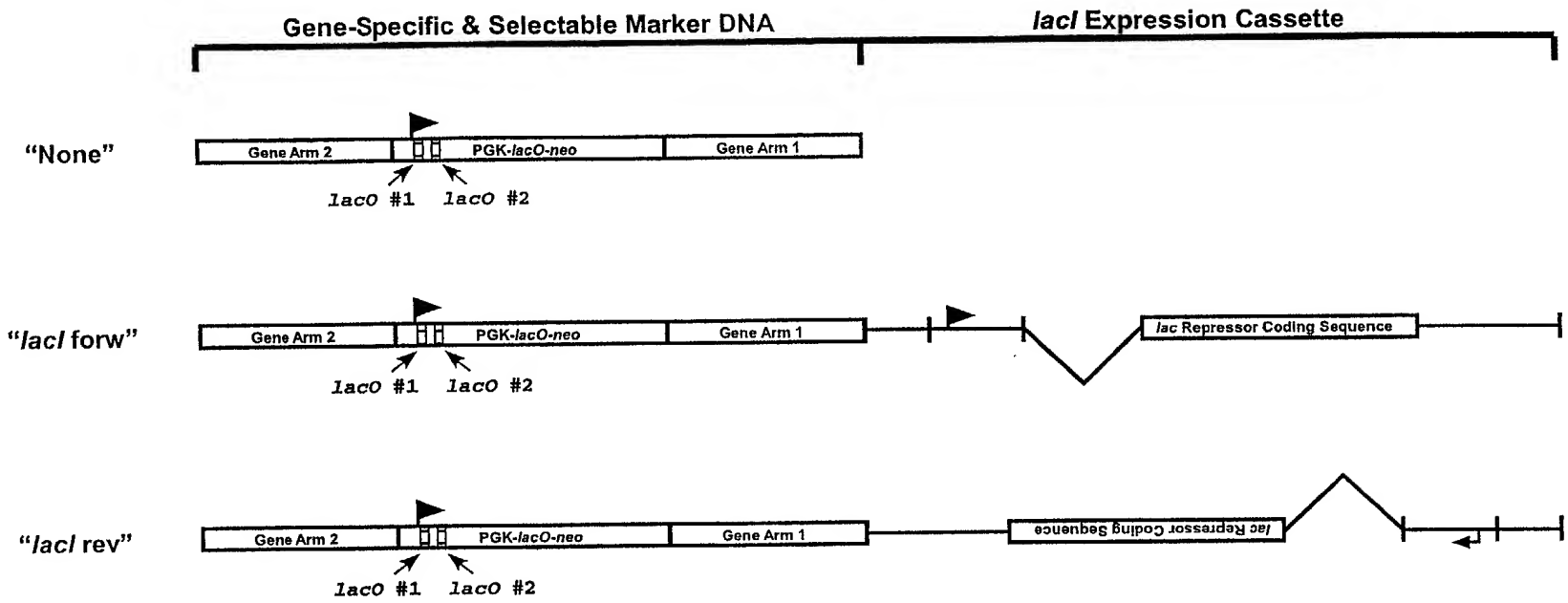

Gene-Specific & Selectable Marker DNA
lacI Expression Cassette
"None"
Gene Arm 2
PGK-lacO-neo
Gene Arm 1
lacO #1
lacO #2
"lacI forw"
Gene Arm 2
PGK-lacO-neo
Gene Arm 1
lac Repressor Coding Sequence
lacO #1
lacO #2
"lacI rev"
Gene Arm 2
PGK-lacO-neo
Gene Arm 1
lacO #1
lacO #2

Figure 11

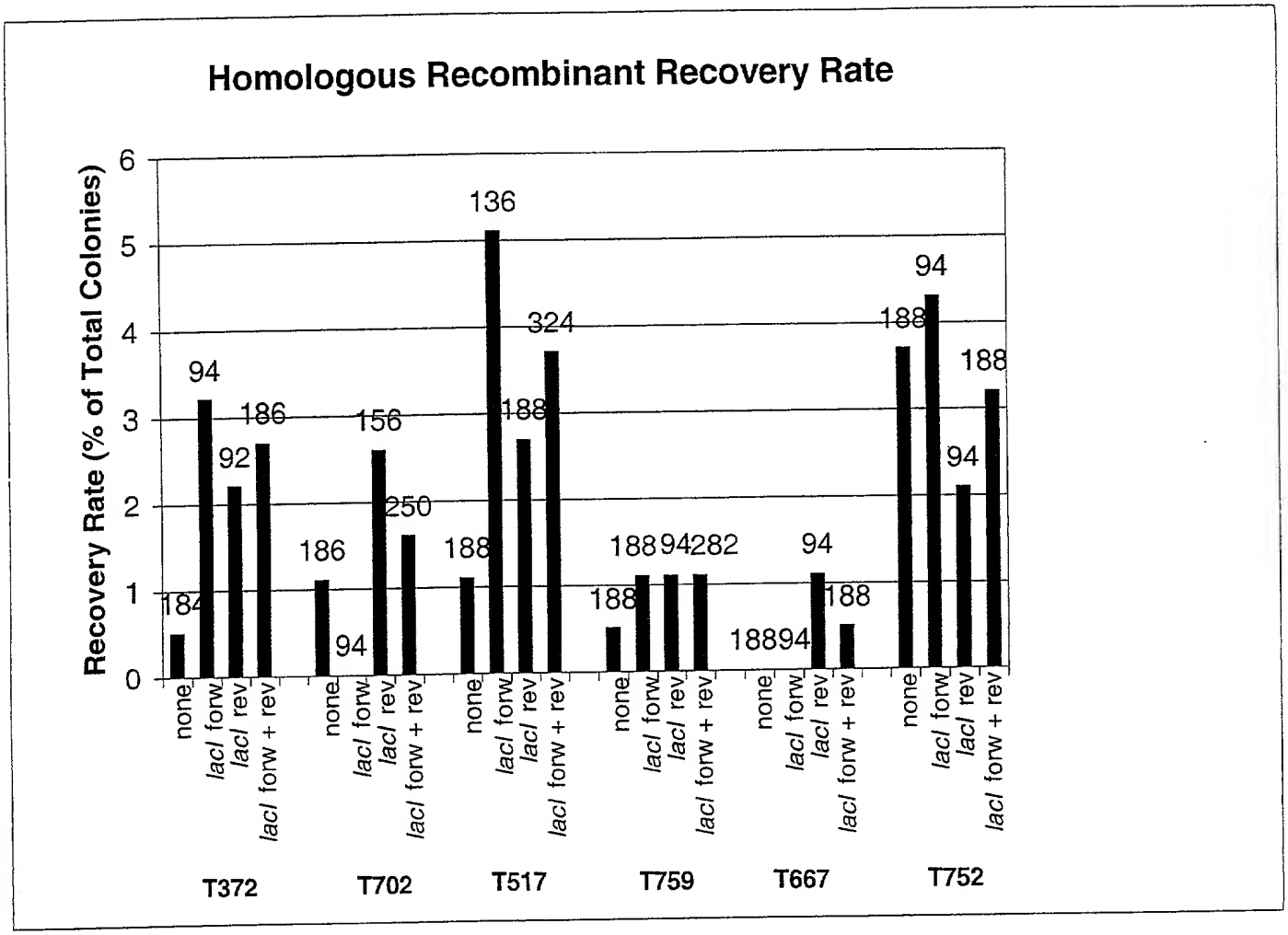

Homologous Recombinant Recovery Rate
Recovery Rate (% of Total Colonies)
0
1
2
3
4
5
6
184
94
92
186
186
94
156
250
188
136
188
324
188
94
282
188
94
188
188
94
94
188
none
lacI forw
lacI rev
lacI forw + rev
T372
T702
T517
T759
T667
T752

Figure 12

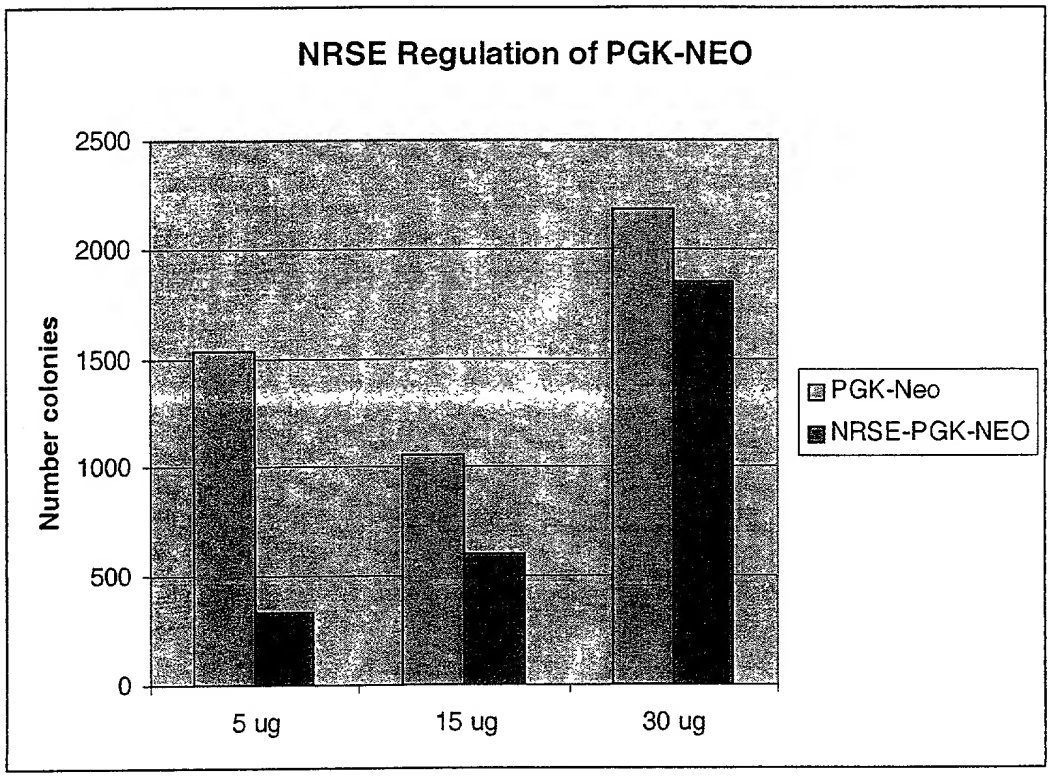


FIGURE 13

GCGGCCGCGAGTCGACGAGGCCGGCCGATTAATTAAGGCTCgacattgattattgactag
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GACCTTACGGGACTTTCCTACTTGGCAGTACATCTACGTATTAGTCATCGCTATTACCAT
GGTtcgaggtgagccccacgttctgcttcactctccccatctccccccccctccccacccc
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TAATGACGGCTCGTTTCTTTTCTGTGGCTGCGTGAAAGCCTTAAAGGGCTCCGGGAGGGC
CCTTTGTGCGGGGGGGAGCGGCTCGGGGGGTGCGTGCGTGTGTGTGTGCGTGGGGAGCGC
CGCGTGCGGCCCGCGCTGCCCGGCGGCTGTGAGCGCTGCGGGCGCGGCGCGGGGCTTTGT
GCGCTCCGCGTGTGCGCGAGGGGAGCGCGGCCGGGGGCGGTGCCCCGCGGTGCGGGGGGG
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GGGGGTGGCGGCAGGTGGGGGTGCCGGGCGGGGCGGGGCCGCCTCGGGCCGGGGAGGGCT
CGGGGGAGGGGCGCGGCGGCCCCGGAGCGCCGGCGGCTGTCGAGGCGCGGCGAGCCGCAG
CCATTGCCTTTTATGGTAATCGTGCGAGAGGGCGCAGGGACTTCCTTTGTCCCAAATCTG
GCGGAGCCGAAATCTGGGAGGCGCCGCCGCACCCCCTCTAGCGGGCGCGGGCGAAGCGGT
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CCCTTCTCCATCTCCAGCCTCGGGGCTGCCGCAGGGGGACGGCTGCCTTCGGGGGGGACG
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TGTTCATGCCTTCTTCTTTTTCCTACAGctcctgggcaacgtgctggttgttgtgctgtc
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GACATATGGGAGGGCAAATCATTTAAAACATCAGAATGAGTATTTGGTTTAGAGTTTGGC
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TTTTTTTTATATTTTGTTTTGTGTTATTTTTTTCTTTAACATCCCTAAAATTTTCCTTAC
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TTCTCTTATGAAGATCcctcgacctgcagcccaagctCGGGGCCAGGTCGGCCGAGCGAT
CGCGAGAATTCGGCTTAAGTGAGTCGTATTACGGACTGGCCGTCGTTTTACAACGTCGTG
ACTGGGAAAACCCTGGCGTTACCCAACTTAATCGCCTTGCAGCACATCCCCCTTTCGCCA
GCTGGCGTAATAGCGAAGAGGCCCGCACCGATCGCCCTTCCCAACAGTTGCGCAGCCTGA

Fig. 14A

ATGGCGAATGGCGCTTCGCTTGGTAATAAAGCCCGCTTCGGCGGGCTTTTTTTTGGTTAA
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AAATACATTCAAATATGTATCCGCTCATGAGACAATAACCCTGATAAATGCTTCAATAAT
ATTGAAAAAGGAAGAGTATGAGTATTCAACATTTCCGTGTCGCCCTTATTCCCTTTTTTG
CGGCATTTTGCCTTCCTGTTTTTGCTCACCCAGAAACGCTGGTGAAAGTAAAAGATGCTG
AAGATCAGTTGGGTGCACGAGTGGGTTACATCGAACTGGATCTCAACAGCGGTAAGATCC
TTGAGAGTTTTCGCCCCGAAGAACGTTCTCCAATGATGAGCACTTTTAAAGTTCTGCTAT
GTGGCGCGGTATTATCCCGTGTTGACGCCGGGCAAGAGCAACTCGGTCGCCGCATACACT
ATTCTCAGAATGACTTGGTTGAGTACTCACCAGTCACAGAAAAGCATCTTACGGATGGCA
TGACAGTAAGAGAATTATGCAGTGCTGCCATAACCATGAGTGATAACACTGCGGCCAACT
TACTTCTGACAACGATCGGAGGACCGAAGGAGCTAACCGCTTTTTTGCACAACATGGGGG
ATCATGTAACTCGCCTTGATCGTTGGGAACCGGAGCTGAATGAAGCCATACCAAACGACG
AGCGTGACACCACGATGCCTGTAGCAATGGCAACAACGTTGCGCAAACTATTAACTGGCG
AACTACTTACTCTAGCTTCCCGGCAACAATTAATAGACTGGATGGAGGCGGATAAAGTTG
CAGGACCACTTCTGCGCTCGGCCCTTCCGGCTGGCTGGTTTATTGCTGATAAATCTGGAG
CCGGTGAGCGTGGGTCTCGCGGTATCATTGCAGCACTGGGGCCAGATGGTAAGCCCTCCC
GTATCGTAGTTATCTACACGACGGGGAGTCAGGCAACTATGGATGAACGAAATAGACAGA
TCGCTGAGATAGGTGCCTCACTGATTAAGCATTGGTAACTGTCAGACCAAGTTTACTCAT
ATATACTTTAGATTGATTTACCCCGGTTGATAATCAGAAAAGCCCCAAAAACAGGAAGAT
TGTATAAGCAAATATTTAAATTGTAAACGTTAATATTTTGTTAAAATTCGCGTTAAATTT
TTGTTAAATCAGCTCATTTTTTAACCAATAGGCCGAAATCGGCAAAATCCCTTATAAATC
AAAAGAATAGCCCGAGATAGGGTTGAGTGTTGTTCCAGTTTGGAACAAGAGTCCACTATT
AAAGAACGTGGACTCCAACGTCAAAGGGCGAAAAACCGTCTATCAGGGCGATGGCCCACT
ACGTGAACCATCACCCAAATCAAGTTTTTTGGGGTCGAGGTGCCGTAAAGCACTAAATCG
GAACCCTAAAGGGAGCCCCCGATTTAGAGCTTGACGGGGAAAGCGAACGTGGCGAGAAAG
GAAGGGAAGAAAGCGAAAGGAGCGGGCGCTAGGGCGCTGGCAAGTGTAGCGGTCACGCTG
CGCGTAACCACCACACCCGCCGCGCTTAATGCGCCGCTACAGGGCGCGTAAAAGGATCTA
GGTGAAGATCCTTTTTGATAATCTCATGACCAAAATCCCTTAACGTGAGTTTTCGTTCCA
CTGAGCGTCAGACCCCGTAGAAAAGATCAAAGGATCTTCTTGAGATCCTTTTTTTCTGCG
CGTAATCTGCTGCTTGCAAACAAAAAAACCACCGCTACCAGCGGTGGTTTGTTTGCCGGA
TCAAGAGCTACCAACTCTTTTTCCGAAGGTAACTGGCTTCAGCAGAGCGCAGATACCAAA
TACTGTTCTTCTAGTGTAGCCGTAGTTAGGCCACCACTTCAAGAACTCTGTAGCACCGCC
TACATACCTCGCTCTGCTAATCCTGTTACCAGTGGCTGCTGCCAGTGGCGATAAGTCGTG
TCTTACCGGGTTGGACTCAAGACGATAGTTACCGGATAAGGCGCAGCGGTCGGGCTGAAC
GGGGGGTTCGTGCACACAGCCCAGCTTGGAGCGAACGACCTACACCGAACTGAGATACCT
ACAGCGTGAGCTATGAGAAAGCGCCACGCTTCCCGAAGGGAGAAAGGCGGACAGGTATCC
GGTAAGCGGCAGGGTCGGAACAGGAGAGCGCACGAGGGAGCTTCCAGGGGGAAACGCCTG
GTATCTTTATAGTCCTGTCGGGTTTCGCCACCTCTGACTTGAGCGTCGATTTTTGTGATG
CTCGTCAGGGGGGCGGAGCCTATGGAAAAACGCCAGCAACGCGGCCTTTTTACGGTTCCT
GGCCTTTTGCTGGCCTTTTGCTCACATGTAATGTGAGTTAGCTCACTCATTAGGCACCCC
AGGCTTTACACTTTATGCTTCCGGCTCGTATGTTGTGTGGAATTGTGAGCGGATAACAAT
TTCACACAGGAAACAGCTATGACCATGATTACGCCAAGCTACGTAATACGACTCACTAG

Fig. 14B